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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,518	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19-21,23,24,28,29,31,33,34,38,39,41,43,46,49 and 54-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19-21,23,24,28,29,31,33,34,38,39,41,43,46,49 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: 2 google define results print outs.

DETAILED ACTION

1. The finality of the office action mailed 3/8/07 is withdrawn.

2. This action is written in response to applicant's correspondence submitted 6/8/07. Claims 1-2, 7-8, 32, 40, 42, 44-45, 47-48, and 50-53 were canceled. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 39, 41, 43, 46, 49, 54, and 55 and have been amended claims 56 has been added. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 39, 41, 43, 46, 49, 54, 55, and 56 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not sufficient to place the claims in condition for allowance for the reasons set forth in this office action. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

3. The claims have basis in parent applications 10/268730 and 09477148, and thus have an effective filing date of at least 1/4/00, except for claims which are rejected in this office action for having new matter relative to the instant application. These claims do not have support in the parent.

4. The examiner was not able to identify basis in the provisional application 60/115,125 for the instantly claimed invention. For example, basis for the limitation that the blood samples have not been fractionated into cell types from subjects was not identified, nor basis for the current claims which recite analysis for each gene in a collection of two or more genes for the same disease, nor for the claims which recite subjects that are symptomatic for disease, nor for quantifying a level of differential expression, nor for quantifying levels of RNA in samples. If

applicant desires priority to the provisional application for the pending claims, applicant should provide description of how each element of the pending claims is supported by the disclosure of the provisional application.

Claim Rejections - 35 USC § 112

5. Claims 19, 21, 24, 29, 31, 33-34, 38, 39, 43, 46, 49, 55, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are indefinite over the recitation "RNA of unfractionated cells of lysed blood samples" because it is not clear how lysed blood samples can still retain cells since lysis destroys the cells. These claims would be clearer if they recited RNA from lysed cells that were not previously fractionated into cell types, or total cellular RNA.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 39 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

Claim 39 requires that "subjects having said disease" in the methods for identifying markers of claims 17, 19, 54 and 55 "have no overt symptoms with respect to said disease."

Claim 46 includes a limitation which appears to be new matter, namely the recitation that "the subjects having said disease are asymptomatic with respect to said disease." These generic claims encompasses the selection of markers in any possible disease. The remarks filed with the amendment points out that there is descriptive support in ¶79 of the specification for the limitation "said subjects having said disease are asymptomatic with respect to said disease" (Paragraph number refers to the numbering in PGPUB US2004/0014059 which is the publication of the parent application). This paragraph clearly teaches that the methods disclosed can be used "for monitoring a patient for the onset of overt symptoms of a disease," but is silent as to a method which uses patients that are asymptomatic for a disease as a means for identifying markers for a disease. Applicant argues that the examiner is requiring a burden that is greater than the requirement of 112 1st paragraph. However, the examiner disagrees, and maintains that she is merely looking to the specification for a written description of the invention as claimed.

The specification provides a single example where differential expression of insulin between control patients, diabetic patients, and a person having asymptomatic diabetes is detected (Example 6, see top of page 36). In this example the specification does not broadly contemplate or suggest that patients asymptomatic for any disease could be used to identify markers for the disease. The specification does not provide any discussion which provides written description for the idea that the disclosed methods could be applied to any patient having a disease but asymptomatic for that disease.

The claim is sufficiently broad so as to make this application to any disease, and the claim requires that "said patient HAVING said disease is asymptomatic for said disease." Applicant argues in the remarks filed 11/14/06 that the analysis of ZFP in the specification

demonstrates using a patient who is asymptomatic for a disease to look for possible markers for a disease. Namely, applicant argues teaching using patients who have diabetes but have not been diagnosed with cardiac hypertrophy or heart failure to look for a potential marker for cardiac hypertrophy and/or heart failure. The claim requires that the patients have the disease but are asymptomatic. The specification, in the ZFP example, does not teach that these diabetes patients HAVE cardiac hypertrophy and/or heart failure but are asymptomatic, as required by the claim. The specification generally suggests that the increased levels of ZFP "may indicate that these subjects are headed in that general direction (¶0058)." Thus, the specification suggests that these subjects may develop the disease, not that they have the disease, as required by the claims. There is no discussion of patients who are "asymptomatic" for heart failure but have heart failure. It is not even clear to the examiner that one could HAVE heart failure but be asymptomatic for heart failure.

Thus, since the specification does not generally describe or discuss the use of asymptomatic patients for marker identification for any or all diseases, as encompassed by the instant claim, this claim is rejected for new matter because the breadth of the claim does not appear to be contemplated in the instant specification.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 39, 41, 46, 49, 54, 55, and 56 are rejected under 35 U.S.C. 102(b) and 102(a) as being anticipated by Ralph et al. (WO 98/24935).

10. Claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 39, 41, 46, 49, 54, 55, and 56 are rejected under 35 U.S.C. 102(e) as being anticipated by Ralph et al. (6190857).

These references have substantially identical disclosures, but are applicable to the instantly claimed invention as of different dates. Both references are applied to the instant claims. In the rejection, column and line numbers from the issued patent are used to refer to the disclosure, but each portion referenced in the patent is also present in the WO document.

Ralph et al. teach that responses secondary to disease states may be reflected in changing patterns of leukocyte mRNA levels that correlate with the presence of the disease state (Col. 5, lines 27-33). Ralph et al. teach the use of RT-PCR to identify two or more markers useful for diagnosing a disease, namely prostate or breast cancer, exemplifying this method for the detection of two transcripts referred to by Ralph et al. as UC331 and UC332, these sequences are RNA encoded by each of two genes (Example 5.6.2 and following, Col. 98). The genes are expressed in blood and non-blood tissues of subjects not having the disease (Col. 101, lines 41-47 and Col. 102, line 5-10). Ralph et al. teach using an oligonucleotide of predetermined sequence which are primers specific to the particular transcripts to detect a presence of the RNA molecules (Col. 98, lines 17-19 and 26-27). Ralph et al. detect a presence in samples from patients having prostate or breast cancer and from healthy volunteers (Col. 98, lines 5-6). Ralph detect the presence of these RNA in DNA-free total RNA from peripheral blood (Col. 98, lines

5-6). DNA-free total RNA from peripheral blood is RNA of a blood samples which have not been fractionated into cell types, and likewise, it is obtained via the lysis of unfractionated cells. Ralph et al. quantify the level of RNA encoded by the genes from both patients having disease and healthy patients, using relative quantitative RT-PCR (Col. 98, line 8). Ralph et al. determine a difference between the levels of RNA in diseased and control samples, said difference identifying the gene as a marker of said disease (Col. 98, lines 32-37). Thus, the disclosure provided by Ralph et al. anticipates instant claims 17, 19, 54, and 55.

Regarding claims 20, 21, 38, and 41 the detecting and quantifying of said RNA is effected by detecting cDNA derived from the RNA, said cDNA being derived from the reverse transcription of RNA (Col. 98, lines 9-10).

Regarding claims 23 and 24, Ralph et al. quantify the control RNA using relative quantitative RT-PCR (Col. 98, line 8).

Regarding claims 28, 29, 31, and 56, Ralph et al. teach quantifying RNA relative to a housekeeping gene (Col. 64, section 4.9.3.3).

Regarding claims 33, the subjects are human (throughout).

Regarding claim 34, the control subjects do not have disease (Col. 98, line 6).

Regarding claims 39 and 46, Ralph et al. teach that their method can be used as a general screening tool for asymptomatic individuals (Col. 61, lines 15-17), and the practice of the method taught by Ralph et al. in this manner would result in the practice of the claimed method.

Regarding claim 49, Ralph et al. teach control subjects with different stages of disease (Col. 61, lines 35-40).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. (WO 98/24953) or Ralph et al. (US 6190857) either taken in view of Sharma et al. (WO 98/49342, as cited in IDS).

The teachings of Ralph et al. are set forth previously in this office action.

Regarding claim 43, Ralph et al. teach that their method may be used to discover disease markers for any disease state that affects the peripheral blood leukocytes, including metastatic or organ defined cancer (Col. 9, line 66- Col. 19, line 3). Ralph et al. do not specifically teach that the disease is colorectal cancer.

Sharma et al. teach that "from the very early stages of disease...the hole organism responds to the changed condition" (p. 19, 4th full ¶), and teaches a methods for identifying two or more markers useful for diagnosing a disease by looking for differentially expressed genes in total RNA isolated from whole blood samples (throughout). Sharma et al. particularly teach that a disease in which their method would be useful is cancer of the bowel (p. 6, 2nd ¶).

Therefore, given the teaching of Ralph et al. that their method would be useful for finding markers in organ defined cancers, and the express teaching of Sharma et al. that differentially expressed markers can be identified in the blood for the detection of bowel cancer, it would have been prima facie obvious to modified the methods taught by Ralph et al. so as to have screened for markers for colorectal cancer as taught by Sharma et al. One would have been motivated to

modify the methods taught by Ralph et al. in order to provide markers for a different type of cancer, following the express suggestion of Ralph et al. that their methods could be used to discover disease markers for disease states which include metastatic or organ defined cancer. Thus, in view of the prior art, the claimed invention is prima facie obvious.

Double Patenting

13. The previously set forth rejections for obviousness type double patenting are maintained and applied to newly added claim 56. Applicant did not provide any arguments particularly traversing these rejections.

Response to Remarks

The previously set forth objections to the claims and rejections under 112 2nd paragraph have been overcome by amendment or cancellation of the claims. A new rejection under 112 2nd paragraph is set forth in this office action.

Regarding the written description rejection for new matter in claims 39 and 46, applicant traverses the rejection. Applicant states that the examiner is concerned because the specification does not disclose how to identify patients who are asymptomatic for a disease. While this may be a concern with the claims, it is not the primary concern. The primary concern is that the specification does not contemplate broadly using subjects asymptomatic for any disease to identify markers for a particular disease. The single example of "asymptomatic" diabetes patients is not sufficient to support an assertion of using any patients that have a disease but are asymptomatic for that disease (any disease) as broadly claimed because this single example does not represent all diseases of any etiology, which breadth is encompassed by the claims.

Applicant states that the examiner suggests that the presence of disease cannot be determined unless the patient has symptoms and that this does not take into account the meaning of the term "symptom." In support of this position, applicant cites a single, narrow definition of the word "symptom." However, the examiner is using a broad, reasonable interpretation of "symptom." Broadly interpreted, a "symptom" can include any indication of disease, including a sign of disease, an unwanted effect of disease, any functional evidence of a disease or condition, any variation in normal or healthy functioning, and others (see Google define: symptom print out attached). Further, "asymptomatic" is broadly interpreted to include without signs or illness or presenting no signs or symptoms of disease (see Google define: asymptomatic print out attached).

The examiner is not suggesting that diagnosing disease in patients described in the literature as "asymptomatic" using objective medical tests was not practiced for some diseases prior to the invention being made. However, in the instant specification, only a single example is given and there is no suggestion of an intention to extrapolate that example to any possible disease, as the instant claims set forth. While the specification sets forth that patients who have no overt symptoms of disease can be subjects for diagnosis or screening using markers previously identified, the specification does not generally set forth that any set of subjects "asymptomatic" for any possible disease can be used to identify markers useful for diagnosing the disease, which is what is claimed in the rejected claims. The rejection is maintained.

The rejection for lack of enablement and lack of written description of claims 1, 2, 20, 21, 23, 24, 28, 29, 31-33, 34, 38, 41, 43, 44, 47, and 48 are withdrawn in view of the cancellation or amendment of these claims.

Rejections over Ringel in view of Kinoshita and Nagai in view of Kephart are overcome by cancellation of the claims or amendment of the rejected claims.

Applicant's arguments regarding Wong et al. in view of Kephart are persuasive, see at least point C(i) in the arguments filed 6/8/07. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Ralph and Ralph in view of Sharma.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are

available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

June 27, 2007